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EXAMINER

STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

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10/03/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/764,186

Applicant(s)

EXNER ET AL.

Examiner

Teresa E. Strzelecka

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

1. Claims 1-6 are pending in the case and will be examined.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite in claim 1. Claim 1 is indefinite over the recitation of "when said probe hybridizes to said HBV nucleic acid", since the preamble states that the method is for the detection of *Borrelia burgdorferi*.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Picken et al. (WO 91/19814), Pahl et al. (J. Clin. Microbiol., vol. 37, pp. 1958-1963, 1999) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claim 1, Picken et al. teach a method of detecting the presence of *B. burgdorferi* in a test sample, comprising:

(a) amplifying FlaA nucleic acids in *Borrelia burgdorferi* nucleic acid sequence if present in said sample using a pair of oligonucleotide primers having the sequences set forth in SEQ ID NO:1 and SEQ ID NO:2 (Picken et al. teach amplifying *Borrelia burgdorferi* nucleic acid sequences using primers selected from the nucleotides 390-712 (page 5, lines 18-33; page 6, lines 1-9) or from the region of nucleotides 475-770 (page 8, lines 20-33; page 9, 10) of the flagellin gene in Fig. 1.);

(b) hybridizing said amplified FlaA nucleic acids with an oligonucleotide probe having the sequence set forth in SEQ ID NO:3, wherein said probe is conjugated to 6-carboxyfluoresceine (FAM) and 6-carboxytetramethylrhodamine (TAMRA), in the presence of an enzyme that cleaves said probe when said probe hybridizes to said HBV nucleic acid (Picken et al. teach detection of the amplicons with a probe selected from the region between nucleotides 585-650 of the flagellin gene in Fig. 1 (page 11, lines 18-33; page 12, lines 1-26).); and

(c) detecting a signal from said probe, wherein said signal indicates the presence or amount of *Borrelia burgdorferi* nucleic acids in said test sample (page 13, lines 31-33; page 16, lines 1-20).

Regarding claim 4, Picken et al. teach samples being blood, cerebrospinal fluid and blood fractions (page 17, lines 1-19).

Regarding claim 5, Picken et al. teach isolation of the nucleic acids prior to amplification (page 17, lines 20-32; page 18, lines 1, 2).

B) Picken et al. teach a region from which primers and probes for the specific detection of *Borrelia burgdorferi* can be obtained, but do not specifically teach sequences with SEQ ID NO: 1-3.

However, as can be seen in the sequence alignment, SEQ ID NO: 1 is identical to nucleotides 581-601 of the flagellin gene in Fig. 1, SEQ ID NO: 2 is identical to nucleotides 688-708, and SEQ ID NO: 3 is identical to nucleotides 631-656, therefore in the region specifically

pointed out by Picken et al. as suitable for the selection of species-specific primers and probes for the detection of *Borrelia burgdorferi*.

Therefore, given the explicit teachings of Picken et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have designed the primers from the region suggested.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of *Borrelia burgdorferi*, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the

primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

C) Neither Picken et al. nor Buck et al. teach a detection probe conjugated to FAM and TAMRA or detection in the presence of an enzyme which cleaves the probe when it hybridizes to the nucleic acid.

D) Pahl et al. teach amplification of *Borrelia burgdorferi* in tissue samples using real-time amplification reaction with the Taq polymerase hydrolyzing the probe during the reaction (Abstract; page 1958, last paragraph; page 1959, first paragraph). They teach primers and a probe selected from the flagellin gene, with primers identical to nucleotides 588-609 and 636-657, and the probe identical to nucleotides 611-634, and the probe labeled with FAM and TAMRA (page 1959, last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the real-time PCR amplification detection of Pahl et al. in the method of detection of *Borrelia burgdorferi* of Picken et al. and Buck et al. The motivation to do so, provided by Pahl et al., would have been that using real-time PCR eliminated the risk of contamination and

reduced labor-intensive detection methods (page 1958, last paragraph; page 1959, first paragraph).

Further, as stated by Pahl et al. (page 1963, last paragraph):

“In summary, we developed a new diagnostic method on the basis of the real-time PCR that allowed for the fast, cost-effective, and easy high-throughput quantification of *B. burgdorferi* in tissue samples. Since we found a good correlation between clinical symptoms and spirochete burden in the mouse model of Lyme disease, we propose this method as a valuable tool in the diagnostics of human Lyme disease.”

6. Claims 2, 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Picken et al. (WO 91/19814), Pahl et al. (J. Clin. Microbiol., vol. 37, pp. 1958-1963, 1999) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999), as applied to claim 1 above, and further in view of Lin (U. S. Patent No. 5,654,179 A), Cruz-Perez et al. (U.S. Patent No. 6,733,999 B2) and Beumer et al. (U.S. Patent No. 5,837,501 A).

A) Regarding claims 2 and 3, Pahl et al. teach co-amplifying the *B. burgdorferi* nucleic acid with β -actin (page 1959, last paragraph), but do not teach human placental DNA as a control.

B) Regarding claims 2, 3 and 6, Lin teaches using human placental DNA as a positive control and adding the human placental DNA to spirochetes before purification of the *B. burgdorferi* nucleic acid (col. 26, lines 39-56; col. 34, lines 60-67; col. 35, lines 1-23). In addition, Lin teaches amplicon with SEQ ID NO: 4, which has nucleotides 180-205 identical to SEQ ID NO: 6 (see sequence alignment), amplified with primers with SEQ ID NO: 2 AND 3 (col. 16, lines 16-22).

Therefore, given the teaching of Lin, it would have been prima facie obvious to select a probe for detection of the positive control of human placental DNA from the sequence with SEQ ID NO: 4 provided by Lin.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed probes simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of human placental DNA, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)."

Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success. Therefore, since a primer is a probe, this analysis applies to the selection of probes as well.

C) Regarding claim 3, Cruz-Perez et al. teach detection of the fungus *S. chartarum* in real-time amplification reaction using an internal control probe labeled with VIC, whereas the probe for the detection of the fungus is labeled with FAM (col. 3, lines 38-55; col. 8, lines 60-67; col. 9, lines 1-7; col. 10, lines 47-67; col. 16, lines 31-67; col. 17, lines 1, 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the probe for the positive internal control of Lin labeled with VIC instead of FAM as suggested by Cruz-Perez et al. The motivation to do so, provided by Cruz-Peraz et al., would have been that the different label allowed differentiation of signals during amplification (col. 10, lines 60-64). It would have been further *prima facie* obvious to use the internal control in the amplification reaction of Picken et al., Buck et al. and Pahl et al. The motivation to do so, provided by Cruz-Perez et al., would have been that the positive control allowed to determine whether polymerization inhibitors were present in the sample (col. 8, lines 60-67; col. 9, lines 1-7).

D) Regarding claim 6, Lin teaches addition of the human placental DNA to the *B. burgdorferi* sample before DNA purification (col. 34, lines 60-67; col. 35, lines 1-23). The motivation to do so, provided by Beumer et al., who teach amplification of viral RNAs and addition of internal control before sample purification (col. 3, lines 62-67; col. 4, lines 1-51), would have been, as stated by Beumer et al. (col. 4, lines 8-16):

"In a preferred embodiment of the invention the nucleic acid constructs are added prior to isolating the nucleic acids from the quantity of test fluid. In this way the loss of nucleic acid that might optionally occur during the isolation procedure will be reflected in both the resulting amounts of analyte nucleic acid and construct nucleic acid present in the sample. The amount of analyte nucleic acid present in original test fluid under investigation can be calculated directly from the obtained results."

7. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**TERESA E. STRZELECKA, PH.D.
PRIMARY EXAMINER**

Teresa Strzelecka
9/29/07